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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,079	11/14/2005	Mark Theodoor Verhaar	0470-051409	5293

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EXAMINER	
CLARK, SARA E	
ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,079	VERHAAR ET AL.	
	Examiner	Art Unit	
	SARA E. CLARK	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-73* is/are pending in the application.

4a) Of the above claim(s) *49-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/9/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL REJECTION

This application is a 35 U.S.C. 371 (national stage) application of PCT/NL03/00782, filed 11/7/2003, which claims benefit of priority to EPO 02079676.9, filed 11/8/2002. Claims 32-73, as amended, are pending.

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 32-48) in the reply filed on 4/24/2009 is acknowledged.

2. Claims 49-73 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/24/2009.

Priority

3. Acknowledgment is made of applicant's claim to foreign priority under 35 U.S.C. 119(a)-(d).

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 1/9/2006 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Claim Objections

5. Claim 35 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 32. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC §112, Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 32-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 32 recites a protecting group C selected from monofunctional aliphatic hydroxyl protecting groups; however, “C” is well-known in the art as the chemical symbol for carbon.

Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process*

Control Corp. v. HydReclaim Corp., 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999).

8. Claims 41-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claims 41-42 recite the abbreviation "PVP." This is ambiguous because the specification provides no definition for the term, and in the chemical arts "PVP" can refer to many different polymers, for example, polyvinylpyrrolidone or poly-4-vinylphenol. For examination purposes, "PVP" is interpreted as poly-4-vinylpyridine, on the basis of Example 9.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

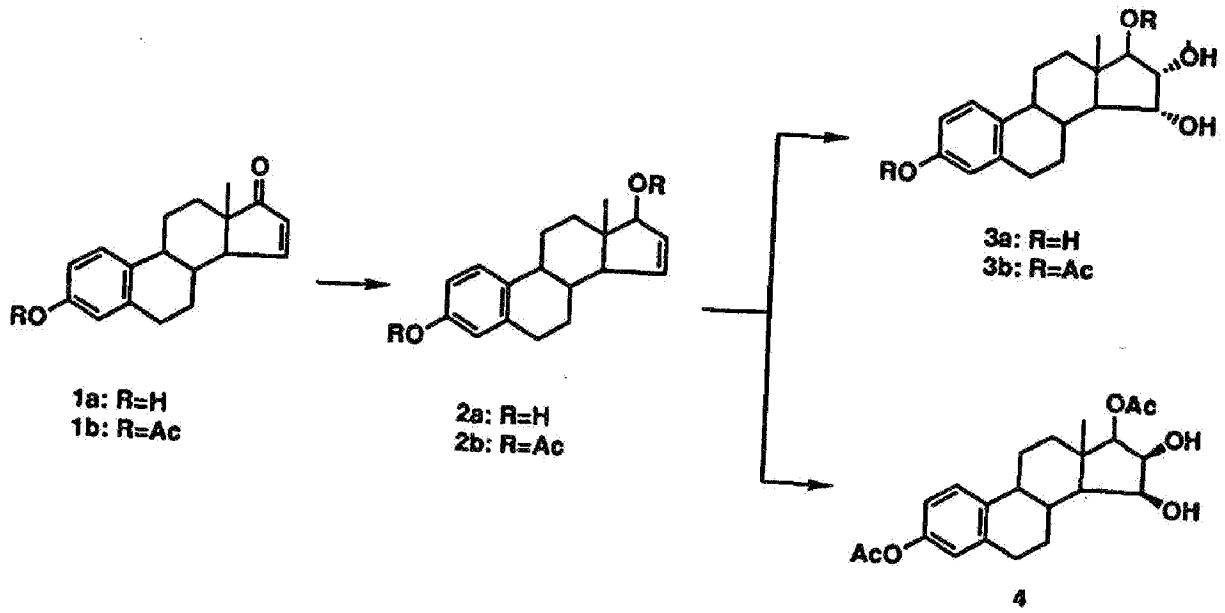
10. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. **Claims 32-38, 40, and 46-48** are rejected under 35 U.S.C. 103(a) as being unpatentable over Suzuki et al. (Steroids 60, 277-284 (1995)) in view of Poirier et al. (Tetrahedron 47(37), 7751-66 (1991) (both provided by Applicant on the IDS dated 1/9/2006), as evidenced by Greene's Protective Groups in Organic Synthesis 3E (1999).

Suzuki et al. disclose a process for the preparation of estra-1,3,5(10)-trien-3,15α,16α,17β-tetraol (a.k.a. estetrol or E4) comprising:

- Starting with estrone, compound (1a), 15-dehydroestrone, is synthesized in five steps;
- Protection of the 3-OH by conversion to 3-OAc to give compound (1b), followed by reduction with $LiAlH_4$ to give compound (2a), 15-dehydroestradiol;
- Protection of the 17-OH by conversion to 17-OAc to give compound (2b);
- Oxidation with OsO_4 to give compound (3b), estra-1,3,5(10)-trien-3,15α,16α,17β-tetraol diacetate (with –OAc protecting groups at the 3 and 17 positions) in 46% yield; (see scheme 1; p. 281, right column, first full paragraph); and
- Deprotection of 3-OAc and 17β-OAc by extraction from ethyl acetate to give compound (3a), estetrol (see p. 278, right column).



Thus, Suzuki et al. disclose a process for

(1) converting estrone into 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one, wherein A is a protecting group (compound 1b);

(2) reducing the 17-keto group to 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol (compound 2a);

(3) protecting the 17-OH group to give 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene, wherein C is a protecting group (compound 2b);

(4) oxidizing the carbon-carbon double bond of ring D (C_{15}=C_{16}) to give 3,17-diprotected estetrol (compound 3b);

(5) and removing the protecting groups A and C to give estetrol,

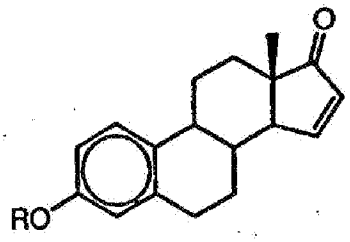
as recited by steps 1, 2, 3, 4, and 5 of claim 32.

Suzuki et al. disclose acetyl as the 17-OH protecting group C, as recited by claims 32, 35, and 36; reduction of the carbonyl (17-keto) group with a metal hydride compound ($LiAlH_4$), as recited by claims 37 and 38; and oxidation of the Δ^{15} double bond with OsO_4, as recited by claim 40.

However, Suzuki et al. do not disclose a 3-OH protecting group A which is a C_1-C_5 alkyl group or a C_7-C_{12} benzylic group; or that the 3-OH protecting group A is removed prior to removing the 17-OH protecting group C, as recited by claim 32.

Poirier et al. disclose the conversion of estrone to estra-1,3,5(10),15-tetraen-17-one according to well-known methodology (p. 7758), followed by protection of the 3-OH group with benzyl or methyl to give 3-benzyloxy-estra-1,3,5(10),15-tetraen-17-one

(compound 8) or 3-methoxy-estra-1,3,5(10),15-tetraen-17-one (compound 9), respectively (p. 7758; scheme 1).



8 R=Bn
9 R=CH_3

Compound (8) corresponds to the claimed compound wherein protecting group A is a benzyl group, as recited by claims 32-34, and compound (9) corresponds to the claimed compound wherein protecting group A is a methyl (C_1-C_5 alkyl) group, as recited by claim 32.

In addition, Poirier et al. disclose the deprotection of the 3-OH protecting group A, corresponding to step 5 as recited by claim 32. Where the 3-OH protecting group A is benzyl, it can be removed by catalytic hydrogenation at atmospheric pressure using hydrogen gas with a palladium/carbon (Pd/C) catalyst (scheme 1, step (f); p. 7755), as recited by claims 46 and 47. Where the 3-OH protecting group A is methyl, it can be removed by using BBr_3 in dichloromethane (scheme 1, step (g)), as recited by claim 48.

Thus, Poirier et al. teach protection of the 3-OH group of D-ring modified estrogens with a benzyl group or with a methyl group, and subsequent deprotection. The 3-O-benzyl- or 3-O-methyl-protected compounds (8) and (9) are disclosed as starting materials for synthesis of C_{15} alkylated steroids, which Poirier et al. carried out by the use of copper-catalyzed conjugate addition of Grignard reagent (p. 7752).

One of ordinary skill in the chemical arts would have been motivated to modify the 3-O-acetate (ester) protecting group disclosed by Suzuki et al. by protecting the 3-OH group with O-methyl or O-benzyl ethers, as taught by Poirier et al., because the following step, reduction with $LiAlH_4$, would cleave the acetate protecting group to yield the unprotected 3-OH (conversion of compound 1b to compound 2a), and requires re-protecting the 3-OH group in the next step (conversion of compound 2a to compound 2b) to survive the reaction conditions of the steps that follow. $LiAlH_4$ is known to reduce esters (such as –OAc) to primary alcohols, while methyl or benzyl 3-OH protecting groups (ethers) would not be reduced by $LiAlH_4$ (see, e.g., attached chart showing that methyl ether and benzyl ether (hydroxyl protecting groups 1 and 26) have low reactivity, i.e., are stable, in the presence of hydride reducing agents including $LiAlH_4$ and $NaBH_4$). Thus, methyl and benzyl ethers would be expected to function as effective 3-OH protecting groups that would obviate the need to subsequently repeat a hydroxyl-protecting step following the metal hydride reduction.

Finally, it is noted that Suzuki et al. disclose the simultaneous cleavage of the 3-OAc and 17-OAc protecting groups by alkaline hydrolysis (conversion of compound 3b to compound 3a, estetrol), rather than separate deprotection steps, namely deprotection of the 3-OH group prior to deprotection of the 17-OH group, as recited by claim 32. However, whereas the 3-OH and 17-OH protecting groups of Suzuki are identical (acetate), it is predictable that distinct deprotection steps may be necessary where the protecting groups are different, as required by the definitions of A and C as recited by claim 32. Further, the specification indicates that the order of the deprotection steps can

be reversed or performed simultaneously with no material change in the final product (WO04/41839, p. 20, lines 17-26). As recognized by MPEP §2144.04, citing *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946), selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results; see also *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (selection of any order of mixing ingredients is *prima facie* obvious).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the synthesis of estetrol from estrone as taught by Suzuki et al. by modifying the 3-OH protecting group from acetate to methyl or benzyl, as taught by Poirier et al. with a reasonable expectation of success, because doing so would eliminate the need to repeat the 3-OH protecting step, simplifying the process.

12. **Claims 32-40 and 46-48** are rejected under 35 U.S.C. 103(a) as being unpatentable over Suzuki et al. and Poirier et al. as evidenced by Greene (1999), as applied to claims 32-38, 40, and 46-48 above, and further in view of Pearlman (USPN 4,739,078) as evidenced by Chemical Land data sheet for $LiAlH_4$.

As discussed above, **Suzuki et al**. (scheme 1) disclose a process for the synthesis of estetrol from estrone, comprising

(1) converting estrone into 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one, wherein A is a protecting group (compound 1b);

(2) reducing the 17-keto group to 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol (compound 2a);

(3) protecting the 17-OH group to give 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene, wherein C is a protecting group (compound 2b);

(4) oxidizing the carbon-carbon double bond of ring D (C_{15}=C_{16}) to give 3,17-diprotected estetrol (compound 3b);

(5) and removing the protecting groups A and C to give estetrol,

as recited by steps 1, 2, 3, 4, and 5 of claim 32.

Suzuki et al. disclose acetyl as the 17-OH protecting group C, as recited by claims 32, 35, and 36; reduction of the carbonyl (17-keto) group with a metal hydride compound ($LiAlH_4$), as recited by claims 37 and 38; and oxidation of the Δ^{15} double bond with OsO_4, as recited by claim 40.

Poirier et al. disclose the conversion of estrone to estra-1,3,5(10),15-tetraen-17-one according to well-known methodology (p. 7758), followed by protection of the 3-OH group with benzyl or methyl to give 3-benzyloxy-estra-1,3,5(10),15-tetraen-17-one (compound 8) or 3-methoxy-estra-1,3,5(10),15-tetraen-17-one (compound 9), respectively (p. 7758; scheme 1). Compound (8) corresponds to the claimed compound wherein protecting group A is a benzyl group, as recited by claims 32-34, and compound (9) corresponds to the claimed compound wherein protecting group A is a methyl (C_1-C_5 alkyl) group, as recited by claim 32.

In addition, Poirier et al. disclose the deprotection of the 3-OH protecting group A, corresponding to step 5 as recited by claim 32. Where the 3-OH protecting group A

is benzyl, it can be removed by catalytic hydrogenation at atmospheric pressure using hydrogen gas with a palladium/carbon (Pd/C) catalyst (scheme 1, step (f); p. 7755), as recited by claims 46 and 47. Where the 3-OH protecting group A is methyl, it can be removed by using BBr_3 in dichloromethane (scheme 1, step (g)), as recited by claim 48.

Thus, Poirier et al. teach the protection and deprotection of the 3-OH group of D-ring modified estrogens with a benzyl group or with a methyl group. The 3-O-benzyl- or 3-O-methyl-protected compounds (8) and (9) are disclosed as starting materials for synthesis of C_{15} alkylated steroids, which Poirier et al. carried out by the use of copper-catalyzed conjugate addition of Grignard reagent (p. 7752).

One of ordinary skill in the chemical arts would have been motivated to modify the 3-O-acetate (ester) protecting group disclosed by Suzuki et al. by protecting the 3-OH group with O-methyl or O-benzyl ethers, as taught by Poirier et al., because the following step, reduction with $LiAlH_4$, would cleave the acetate protecting group to yield the unprotected 3-OH (conversion of compound 1b to compound 2a), and requires re-protecting the 3-OH group in the next step (conversion of compound 2a to compound 2b) to survive the reaction conditions of the steps that follow. $LiAlH_4$ is known to reduce esters (such as –OAc) to primary alcohols, while methyl or benzyl 3-OH protecting groups (ethers) would not be reduced by $LiAlH_4$ (see, e.g., Greene, disclosing that methyl ether and benzyl ether (hydroxyl protecting groups 1 and 26) have low reactivity, i.e., are stable, in the presence of hydride reducing agents including $LiAlH_4$ and $NaBH_4$). Thus, methyl and benzyl ethers would be expected to function as effective 3-OH

protecting groups that would obviate the need to subsequently repeat a hydroxyl-protecting step following the metal hydride reduction.

It is noted that Suzuki et al. disclose the simultaneous cleavage of the 3-OAc and 17-OAc protecting groups by alkaline hydrolysis (conversion of compound 3b to compound 3a, estetrol), rather than separate deprotection steps, namely deprotection of the 3-OH group prior to deprotection of the 17-OH group, as recited by claim 32. However, whereas the 3-OH and 17-OH protecting groups of Suzuki are identical (acetate), it is predictable that distinct reagents for each deprotection step may be necessary where the protecting groups are different, as required by the definitions of A and C as recited by claim 32. Further, the specification indicates that the order of the deprotection steps can be reversed or performed simultaneously with no material change in the final product (WO04/41839, p. 20, lines 17-26). As recognized by MPEP §2144.04, citing *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946), selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results; see also *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (selection of any order of mixing ingredients is *prima facie* obvious).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the synthesis of estetrol from estrone as taught by Suzuki et al. by modifying the 3-OH protecting group from acetate to methyl or benzyl, as taught by Poirier et al. with a reasonable expectation of success, because doing so would eliminate the need to repeat the 3-OH protecting step, simplifying the process.

However, Suzuki et al. and Poirier et al. do not disclose reduction of the 17-keto group with $NaBH_4$ in combination with $CeCl_3$ hydrate ($NaBH_4/CeCl_3$), as recited by claim 39.

Pearlman et al. disclose a method of stereoselectively reducing carbonyl groups of biologically important prostaglandin intermediates (abstract), in particular under Luche conditions (that is, by the use of $NaBH_4/CeCl_3$) (col. 4, lines 13-14 and 26-27; Example 1; Table 1). A prostaglandin enone is treated with a borohydride salt (e.g., sodium borohydride) and a lanthanide salt (e.g., cerium trichloride) in an inert solvent at a low temperature to give a high yield of the corresponding 15α-hydroxy epimer (col. 6, line 67 to col. 7, line 5).

In addition, Pearlman et al. disclose that suitable protecting groups for other functional groups on the molecule include any group capable of surviving the conditions of the reaction, to include a group which replaces a hydroxy hydrogen (col. 4, lines 32-35), such as acyl or benzyl (col. 5, lines 4-10). As evidenced by, for example, the attached Chemical Land data sheet, $LiAlH_4$ is a powerful reducing agent which can be used to reduce esters, but $NaBH_4$ is a milder reducing agent that does not react with esters. Thus, Pearlman discloses that acyl or benzyl protecting groups can be used equivalently where $NaBH_4$ is the reducing agent, buttressing the motivation provided by Poirier et al. to modify the 3-O-acetyl protecting group of Suzuki et al. to 3-O-benzyl.

One of ordinary skill in the chemical arts would have been motivated to modify the reduction reagent of Suzuki et al. ($LiAlH_4$) by employing Luche reduction conditions ($NaBH_4/CeCl_3$) to reduce the 17-keto group of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-

one, because ring D is an enone (Δ^{15}, 17-keto), and Pearlman teaches that $NaBH_4$ in $CeCl_3$ is effective for the stereoselective reduction of enone carbonyl groups to yield predominantly one epimer over the other (see Table IV). $NaBH_4$ in $CeCl_3$ would have been predicted to selectively convert the 17-carbonyl group to 17β-hydroxy because (1) the C_{18} methyl group is in β-orientation, which would be expected to create steric hindrance above the plane of the D ring (flattened due to the Δ^{15} double bond), so that the metal hydride would preferentially add hydrogen to the α-face, placing the reduced hydroxyl group in β-orientation; and (2) $CeCl_3$ enhances the stereoselectivity of the reaction by coordinating with the solvent (such as methanol).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the synthesis of estetrol disclosed by Suzuki et al., as modified by Poirier et al., by employing $NaBH_4$ in $CeCl_3$ rather than $LiAlH_4$ as the 17-keto metal hydride reducing agent, as taught by Pearlman, with a reasonable expectation of success, because (1) the Luche reduction was known to be effective in the stereoselective reduction of biologically important enone intermediates with higher yields of the desired epimer, and (2) Pearlman teaches that benzyl is a suitable hydroxyl-protecting group capable of withstanding the reaction conditions.

13. **Claims 32-38 and 40-48** are rejected under 35 U.S.C. 103(a) as being unpatentable over Suzuki et al. and Poirier et al. as evidenced by Greene (1999), as applied to claims 32-38, 40, and 46-48 above, and further in view of Cainelli et al. (Synth. Comm. Pp. 45-47 (1989), provided by Applicant on the IDS dated 1/9/2006).

As discussed above, **Suzuki et al**. (scheme 1) disclose a process for the synthesis of estetrol from estrone, comprising

(1) converting estrone into 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one, wherein A is a protecting group (compound 1b);

(2) reducing the 17-keto group to 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol (compound 2a);

(3) protecting the 17-OH group to give 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene, wherein C is a protecting group (compound 2b);

(4) oxidizing the carbon-carbon double bond of ring D (C_{15}=C_{16}) to give 3,17-diprotected estetrol (compound 3b);

(5) and removing the protecting groups A and C to give estetrol,

as recited by steps 1, 2, 3, 4, and 5 of claim 32.

Suzuki et al. disclose acetyl as the 17-OH protecting group C, as recited by claims 32, 35, and 36; reduction of the carbonyl (17-keto) group with a metal hydride compound ($LiAlH_4$), as recited by claims 37 and 38; and oxidation of the Δ^{15} double bond with OsO_4, as recited by claim 40.

Poirier et al. disclose the conversion of estrone to estra-1,3,5(10),15-tetraen-17-one according to well-known methodology (p. 7758), followed by protection of the 3-OH group with benzyl or methyl to give 3-benzyloxy-estra-1,3,5(10),15-tetraen-17-one (compound 8) or 3-methoxy-estra-1,3,5(10),15-tetraen-17-one (compound 9), respectively (p. 7758; scheme 1). Compound (8) corresponds to the claimed compound wherein protecting group A is a benzyl group, as recited by claims 32-34, and

compound (9) corresponds to the claimed compound wherein protecting group A is a methyl (C_1-C_5 alkyl) group, as recited by claim 32.

In addition, Poirier et al. disclose the deprotection of the 3-OH protecting group A, corresponding to step 5 as recited by claim 32. Where the 3-OH protecting group A is benzyl, it can be removed by catalytic hydrogenation at atmospheric pressure using hydrogen gas with a palladium/carbon (Pd/C) catalyst (scheme 1, step (f); p. 7755), as recited by claims 46 and 47. Where the 3-OH protecting group A is methyl, it can be removed by using BBr_3 in dichloromethane (scheme 1, step (g)), as recited by claim 48.

Thus, Poirier et al. teach the protection and deprotection of the 3-OH group of D-ring modified estrogens with a benzyl group or with a methyl group. The 3-O-benzyl- or 3-O-methyl-protected compounds (8) and (9) are disclosed as starting materials for synthesis of C_{15} alkylated steroids, which Poirier et al. carried out by the use of copper-catalyzed conjugate addition of Grignard reagent (p. 7752).

One of ordinary skill in the chemical arts would have been motivated to modify the 3-O-acetate (ester) protecting group disclosed by Suzuki et al. by protecting the 3-OH group with O-methyl or O-benzyl ethers, as taught by Poirier et al., because the following step, reduction with $LiAlH_4$, cleaves the acetate protecting group to yield the unprotected 3-OH (conversion of compound 1b to compound 2a), and requires re-protecting the 3-OH group in the next step (conversion of compound 2a to compound 2b) to survive the reaction conditions of the steps that follow. $LiAlH_4$ is known to reduce esters (such as –OAc) to primary alcohols, while methyl or benzyl 3-OH protecting groups (ethers) would not be reduced by $LiAlH_4$ (see, e.g., Greene, disclosing that

methyl ether and benzyl ether (hydroxyl protecting groups 1 and 26) have low reactivity, i.e., are stable, in the presence of hydride reducing agents including $LiAlH_4$ and $NaBH_4$). Thus, methyl and benzyl ethers would be expected to function as effective 3-OH protecting groups that would obviate the need to subsequently repeat a hydroxyl-protecting step following the metal hydride reduction.

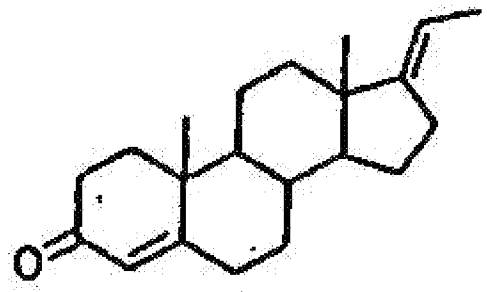
It is noted that Suzuki et al. disclose the simultaneous cleavage of the 3-OAc and 17-OAc protecting groups by alkaline hydrolysis (conversion of compound 3b to compound 3a, estetrol), rather than separate deprotection steps, namely deprotection of the 3-OH group prior to deprotection of the 17-OH group, as recited by claim 32. However, whereas the 3-OH and 17-OH protecting groups of Suzuki are identical (acetate), it is predictable that distinct reagents for each deprotection step may be necessary where the protecting groups are different, as required by the definitions of A and C as recited by claim 32. Further, the specification indicates that the order of the deprotection steps can be reversed or performed simultaneously with no material change in the final product (WO04/41839, p. 20, lines 17-26). As recognized by MPEP §2144.04, citing *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946), selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results; see also *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (selection of any order of mixing ingredients is *prima facie* obvious).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the synthesis of estetrol from estrone as taught by Suzuki et al. by modifying the 3-OH protecting group from acetate to

methyl or benzyl, as taught by Poirier et al. with a reasonable expectation of success, because doing so would eliminate the need to repeat the 3-OH protecting step, simplifying the process.

However, Suzuki et al. and Poirier et al. do not disclose oxidation of the Δ^{15} double bond with a catalytic amount of OsO_4 immobilized on PVP in combination with trimethylamine-N-oxide, as recited by claims 41-45.

Cainelli et al. disclose a method of catalytic hydroxylation of olefins with catalytic amounts of OsO_4 in combination with trimethylamine-N-oxide, a secondary oxidant which continuously regenerates the tetroxide (p. 45). In addition, Cainelli et al. teach the use of OsO_4 linked to poly-4-vinylpyridine (PVP) in the presence of trimethylamine-N-oxide, which was found to achieve the best results, fast reaction rate, and high yields in the hydroxylation of olefin substrates (p. 46, left column). While not exemplified, Cainelli et al. suggest the utility of OsO_4-PVP/trimethylamine-N-oxide in the *cis*-hydroxylation of steroidal double bonds, such as the 17(20)-double bond of compound 5,



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One of ordinary skill in the chemical arts would have been motivated to modify the oxidizing agent OsO_4 as disclosed by Suzuki et al. by linking it to PVP, employing it with the co-oxidant trimethylamine-N-oxide, and using it in only catalytic amounts, as

taught by Cainelli et al., because the modifications taught by Cainelli et al. require less of the expensive and dangerous reagent OsO_4 while improving reaction time and yield (p. 46, right column), and simplifying separation from the reaction medium (p. 45).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the synthesis of estetrol disclosed by Suzuki et al., as modified by Poirier et al., by reducing the Δ^{15} double bond with only catalytic amounts of OsO_4 linked to PVP in the presence of trimethylamine-N-oxide, as taught by Cainelli et al., with a reasonable expectation of success, because OsO_4 was known as the reagent of choice for converting alkenes to *cis*-diols (such as the C_{15}-C_{16} double bond of 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene), and the modifications disclosed by Cainelli et al. improve safe handling of OsO_4 and achieve better yields of the hydroxylated product.

Conclusion

Claims 32-48 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-7672. The examiner can normally be reached on Mon - Thu, 7:30 am - 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass, can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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